https://doi.org/10.24123/kesdok.v6i2.7305

Case Report

A Case Report Capecitabine-Induce Grade II Hand and Foot Syndrome

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Abstract—*Capecitabine has a common side effect of hand and foot syndrome (HFS). It is cutaneous capecitabine's adverse effect, which generally occurs within 11 to 360 days. In this case report assesses the delayed onset of capecitabine because HFS did not occur within 11-360 days but rather took longer, specifically 720 days. A female patient of 82 years old with a history of breast cancer was diagnosed four years ago. She did not undergo radiation and surgery, only capecitabine tablets as neoadjuvant therapy since April 2021. In August 2023, the patient complained of pain, dryness, and blood in both legs. Analysis of side effects of the drug was carried out using the Naranjo Probability Scale. Therapy management during hospitalization involves stopping capecitabine and performing wound care by applying fusidic acid cream and the patient's complaints improved on the eleventh day of therapy. Capecitabine discontinuation is the most effective strategy to minimize the effect of HFS. Further research is to determine the effectiveness of emollient application as a prevention for HFS.*

Keywords: *adverse effects, capecitabine, hand and foot syndrome*

Abstrak—Sindrom tangan dan kaki efek samping yang sering terjadi pada penggunaan kapesitabine. Efek samping ini merupakan efek samping pada kulit yang terjadi dalam jangka waktu 11 hingga 360 hari. Pada *case report* ini efek samping tidak terjadi dalam jangka waktu 11-360 hari, terjadi keterlambatan reaksi yang berlangsung pada 720 hari setelah penggunaan kapesitabin. Seorang pasien perempuan berusia 82 tahun dengan riwayat kanker payudara didiagnosis empat tahun lalu. Pasien tidak menjalani radiasi dan operasi, hanya mengonsumsi tablet kapesitabin sebagai terapi neoadjuvan sejak April 2021. Pada Agustus 2023, pasien mengeluhkan nyeri, kulit kering, dan berdarah pada kedua kakinya. Analisis efek samping obat dilakukan dengan menggunakan Skala Probabilitas Naranjo. Penatalaksanaan terapi selama rawat inap meliputi penghentian kapesitabin dan perawatan luka dengan krim asam fusidat dan keluhan pasien membaik di hari ke-11 terapi. Penghentian kapesitabin merupakan strategi yang paling efektif untuk meminimalkan efek HFS. Penelitian selanjutnya adalah untuk menentukan efektivitas pemberian emolien sebagai pencegahan HFS.

Kata kunci*: efek samping, kapesitabin, sindrom kaki dan tangan*

INTRODUCTION

Hand and foot syndrome (HFS) is a side effect of cutaneous capecitabine that is affected by the accumulative dose. Although not life-threatening, it can affect the quality of life. Capecitabine is an anti-cancer drug that has been enzymatically transformed into active 5-fluorouracil in cancer cells. FDA has standardized for monotherapy or combination in advanced breast cancer-resistant paclitaxel and anthracycline regimens for capecitabine. Capecitabine was an alternative to fluorouracil infusion because it had selective activity within the tumour, had a low incidence of systemic toxicity, and was easy to administer orally. HFS is the most common side effect reported in 45 to 56% of patients. In another case, HFS occurs within 11 to 360 days, but in this case, HFS arises after 720 days (two years) of capecitabine. The data on hand-foot syndrome was collected using a time series followed by an analysis using the Naranjo Probability Scale.

CASE DESCRIPTION

A Female patient of 82 years old with a history of heart rhythm disturbances with the treatment of amiodarone tablets and grade III osteoarthritis came to the hospital with complaints of pain and a lump in the left breast. In April 2021, breast cancer was diagnosed.

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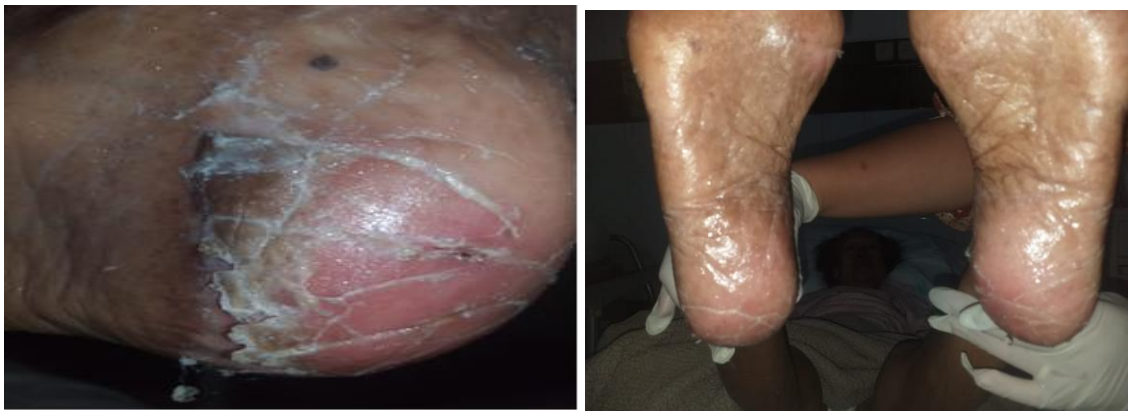
She did not undergo radiation and surgery. The doctor offered to administer a regimen of paclitaxel and anthracycline injections but the patient declined, so the patient only had capecitabine tablets taken two times a day, 1000 mg-0-500 mg, as neoadjuvant therapy. The treatment improved her condition, as evidenced by the doctor's assessment. In the second year of treatment (April 2023), the patient often complained of feeling dizzy until she fell in the bathroom. She was admitted to the hospital and was treated for six days. She was diagnosed with an electrolyte imbalance, sepsis, anaemia with sodium chloride 3%, intravenous antibiotic and an electrolyte tablet.

On physical examination, she appears thin, weighing 39 kg, and can only walk with assistance. She described pain when walking as 7/10 as per the WHO pain scale. The results of the X-ray radiography show a grade III osteoarthritis of the right knee with an inflammatory process. In April 2021, she was started on palliative chemotherapy with capecitabine to be taken at 1500 mg/day for two weeks every 21 days. For the past three years, the patient also took amiodarone tablets to manage arrhythmia, and until now, it has improved. In August 2023, the patient returned to the hospital with pain, dryness, and bloodiness in both legs. A few months earlier, the patient felt dry, cracked hands and legs and dysesthesia when the legs stabbed on the floor.



(A) **(B)**

Figure 1. The leg after capecitabine. Capecitabine's side effects during the therapy (A) and after the capecitabine discontinuation (B).

DISCUSSION

Capecitabine is not an anti-cancer drug but becomes an anti-cancer after capecitabine's prodrug of fluorouridine, which is enzymatically transformed to 5-fluorouracil (5-FU) in the cancer cell [1]. The benefit of capecitabine compared to fluorouracil was that it had selective activity within the tumour, had a low incidence of systemic toxicity, and was easy to administer orally [2]. In metastatic breast cancer (MBC), single-agent capecitabine is more effective than 5-FU infusion, gemcitabine, or vinorelbine. FDA standardizes it for monotherapy or combination in the advanced stage or MBC resistance on paclitaxel and anthracycline regimens [3],[4]. According to CREATE-X, capecitabine for monotherapy has five years of disease-free survival. This study evaluated the addition of adjuvant capecitabine for patients who had a history of neoadjuvant chemotherapy with anthracycline, taxane, or both and did not have a complete pathologic response in a population of patients with HER2-negative breast cancer [4].

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Table 1
Naranjo Adverse Drug Reaction Probability Scale

No	Question	Yes	No	Don't Know	Score
1	Are there any reports of similar side effect?	(+1)	0	0	1
2	Did the side effect occur after the suspected drug was given	(+2)	-1	0	2
3	Did the side effect improve after the drug was stopped or a specific antagonist was given?	(+1)	0	0	1
4	Did the side effect reappear after the drug was readministered?	+2	-1	(0)	0
5	Are there alternative causes that explain the possible side effect?	-1	(+2)	0	2
6	Did the side effect reappear when a placebo was administered?	-1	0	(0)	0
7	Was the drug in the blood (or other fluids) in a concentration known to be toxic?	+1	(0)	0	0
8	Was the reaction more severe when the dose was increased, or slightly severe when the dose was reduced?	+1	0	(0)	0
9	Did the patient have a similar effect or similar drugs in any previous exposure?	+1	0	(0)	0
10	Was the side effect confirmed by the objective evidence?	+1	0	(0)	0
	Total Score				**6**

Hand and foot syndrome (HFS) is the most common adverse effect of capecitabine use-related to dose-limiting in addition to diarrhea and hyperbilirubinemia [5,6]. HFS is also called palmar–plantar erythrodysesthesia [7]. The pathogenesis of capecitabine HFS is still unknown. There are several mechanisms known that capecitabine causes HFS, i.e., overexpression of COX-2 in the legs and hands stimulated by capecitabine and its metabolites. Another hypothesis is that the expression of thymidine phosphorylase (TP) increases 3-10 times as much as in normal cells, where TP will be used to convert from the prodrug form capecitabine to active 5FU [8]. TP to be more highly concentrated in the palms [12]. The second hypothesis is that the eccrine system can eliminate capecitabine. In the hands and feet, there is an increase in the number of eccrine glands, increased vascularization, pressure, and temperature [15].

A few months earlier, the patient had complaints of skin drying, cracking, erythema with a symmetrical tendency, and pain up to peeling. Two days before being hospitalized, the complaints worsened with pain in both legs, redness to exhaust of fluid until bleeding, and a diagnosis of hand and foot syndrome grade two. Within a few days, it will develop into pain like burning, obvious edema, and erythema with a tendency to be symmetrical and peeling and a limitation of daily activity. Extreme cases involve ulcers, scratches, palmar-plantar keratoderma, nail dystrophy, and inflammation of keratosis [9]. The Naranjo Probability Scale was used to analyze capecitabine's side effects (**Table 1**). The score obtained six, indicating probable.

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Table 2
Naranjo Adverse Drug Reaction Probability Scale

Adverse event grade	During Therapy	Dose reduction for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interrupt until resolved to grade 0/1	Maintain dose level
Second appearance	Interrupt until resolved to grade 0/1	25%
Third appearance	Interrupt until resolved to grade 0/1	50%
Fourth appearance	Discontinue treatment permanently	
Grade 3		
First appearance	Interrupt until resolved to grade 0/1	25%
Second appearance	Interrupt until resolved to grade 0/1	50%
Third appearance	Discontinue treatment permanently	
Grade 4		
First appearance	Discontinue treatment permanently OR Interrupt until resolved to grade 0/1 if the clinician deems it to be in the patient's best interest to continue therapy	50%

Severity of HFS can be assessed based on the evaluation of physical changes and the presence of pain. Classification of severity HFS grading systems are commonly used by four grade for The World Health Organization (WHO) and three grades for the National Cancer Institute (NCI) [10,11,12]. Many studies exposed HFS appearing after capecitabine administration. HFS in all grades was reporting occur in 43-71% of capecitabine [13]. About 2-24% of the incidence of HFS when given at a dose from 850 to 1000 mg/m^2 twice a day, while grade 3 HFS occurred in the range of 0–21% with combination regimens in the elderly population [11]. At this dose of capecitabine, HFS occurs in 18–64% of patients, while in grades 3 and 4, changes occur in 8%–24% of patients [16]. Occurrence and severity of HFS are dependent upon dose-related and a higher cumulative dose [14]. Patients had been receiving capecitabine therapy at a cumulative dose of 1500 mg/day. The dose is still in line with the FDA approved for MBC is 1250 mg/m^2, given orally twice daily for two weeks on a 21-day cycle [17]. Meanwhile, in this patient, capecitabine induces HFS that occurs for more than two years, whereas, in systematic reviews, capecitabine induces HFS that occurs in the range of 11 to 360 days [18]. Several factors are involved, such as patient weight, previous cycles of chemotherapy, and other factors that cannot be extracted from the case reports. Implementation of the management of HFS depends on the degree of severity. There are no longitudinal studies specific to HFS therapy from capecitabine, but some studies indicate that dose interruption or discontinuation is an effective strategy to reduce HFS (**Table 2**) [12,19]. In

this patient, the moisturizing agent was given besides the discontinuation of capecitabine. After eleven days of follow-up, skin lesions were reported to have improved symptoms. This is also supported by a scoping review study by Reis et al., 2023, which found that using moisturizing agents can reduce the incidence of HFS [20,21,22].

CONCLUSION

Capecitabine is an oral chemotherapy that often causes side effects. In this patient assesses the delayed onset of capecitabine because HFS did not occur within 11-360 days but rather took longer, specifically 720 days. It can be concluded that the onset of hand and foot syndrome is vary. These side effects can be overcome after eleventh days stopping the capecitabine use and performing wound care by applying fusidic acid cream.

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